Remarks

Applicants thank the Examiner for discussing the rejections and the claims during the telephone conference on July 25, 2006. Applicants have amended the claims in view of the helpful comments provided by the Examiner during this discussion.

Amendments to the Specification

The abstract was amended to reduce the number of words in the abstract to 150 words, as requested by the Examiner. The specification was amended to delete the chemical structure on page 9 of the application and replace it with the correct chemical structures in accordance with the description of the structure on page 10, lines 1-22.

Rejection Under 35 U.S.C. § 102

Claims 33, 34, and 36 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,352,461 to Feldstein *et al.* ("Feldstein"). Claims 33-35 and 37-38 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,503,852 to Steiner *et al.* ("Steiner"). Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

Legal Standard

The standard for lack of anticipation is one of strict identity. To anticipate a claim for a patent, a single prior art source must contain all of the claimed elements. Federal Circuit decisions repeatedly emphasize that anticipation is established only if the following three standards are met: (1) all the elements of an invention, as stated in a patent claim, (2) are identically set forth, (3) in a single prior art reference. *See e.g. Transclean Corp. v. Bridgewood*

Services, Inc., 290 F.3d 1364, 62 U.SP.Q.2d 1865 (Fed. Cir. 2002); *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350, 60 U.S.P.Q.2d 1423 (Fed. Cir. 2001).

The claimed methods

Independent claim 33 as amended defines a method for delivering monomeric or dimeric insulin to a patient in need thereof. The method includes administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative. The delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative. The diketopiperazine derivative has the formula, 2,5-diketo3,6-di(4-X-aminobutyl)piperazine, where X is fumaryl, succinyl, maleyl, or glutaryl. Claim 34 has been canceled and its limitations have been incorporated into independent claim 33. Support for additional amendments to claim 33 can be found in the specification at least at page 12, lines 9-11 and 17-18 (formula for diketipiperazine derivative) and page 16, lines 3-8 and 10-12 (diketopiperazine microparticles).

a. U.S. Patent No. 5,352,461 to Feldstein et al. ("Feldstein")

Feldstein describes a drug delivery system based on the formation of diketopiperazine microparticles by precipitation due to a change in pH. The microparticles can be formed in the presence of a drug to be delivered, which results in the diketopiperazine physically entrapping the drug (abstract). Feldstein does not disclose complexing insulin to a diketopiperazine microparticle or delivery of monomeric or dimeric insulin, as required by claim 33, as amended.

The Examiner points to Example 2, which describes encapsulating porcine insulin by co-precipitation with a diketopiperazine derivative to form microparticles encapsulating insulin (col. 10, lines 38-47). Example 2 describes encapuslating the insulin in a diketopiperazine microparticle at the same time that the microparticle is formed. However, Example 2 does not describe preparing a complex as by, for example, first forming diketopiperazine microparticles, and then complexing them with insulin.

The Examiner alleges that the term "complexed" can be "understood to read on covalent and non-covalent interactions between the diketopiperazine and insulin, including encapsulation." (Office Action, at pages 3 and 4) A typical dictionary definition of the term "complex" is the formation of complex chemical species by the coordination of groups of atoms termed ligands to a central ion, commonly a metal ion. (*see e.g.* enclosed printout from Wikipedia, http://en.wikipedia.org) Generally, the ligand coordinates by providing a pair of electrons that forms an ionic or covalent bond to the central ion (*see* the attached definition from the corrosion and materials technology website). "Encapsulation" as generally used in the art does not require a specific interaction between an agent and the particle in which it is encapsulated. "Encapsulation" refers generally to the physical containment of a drug within or throughout a microparticle (*see e.g.* Feldstein at col. 3, lines 14-21). While encapsulation processes can involve complexation, the mere use of the term "encapsulation" does not indicate a particular chemical interaction between the drug and the material forming the microparticle. In contrast, the claims as amended specify that the delivery formulation is prepared by complexing

the insulin with microparticles of the diketopiperazine derivative. Accordingly, independent claim 33, and dependent claims 34 and 36 are novel over Feldstein.

b. U.S. Patent No. 5,503,852 to Steiner et al. ("Steiner")

Like Feldstein discussed above, Steiner also describes a method for encapsulating an active agent in diketopiperazine microparticles, using co-precipitation to capture the agent within the diketopiperazine precipitate (col. 9, line 55 to col. 10, lines 8). Like Feldstein, Steiner does not disclose complexing insulin to microparticles of the diketopiperazine derivative or delivery of monomeric or dimeric insulin, as required by claim 33, as amended.

The Examiner points to Example 3, which discloses encapsulating porcine insulin by co-precipitation with a diketopiperazine derivative to form microparticles encapsulating insulin. Example 3 describes encapuslating the insulin in a diketopiperazine microparticle at the same time that the microparticle is formed. However, Example 3 does not describe preparing a complex as by, for example, first forming diketopiperazine microparticles, and then complexing them with insulin.

As discussed above, the mere use of the term "encapsulation" does not indicate a specific interaction between an agent and the particle in which it is encapsulated. In contrast, "complex" is typically used to refer to the formation of complex chemical species by the coordination of groups of atoms to a central ion, commonly a metal ion, such as when a ligand provides a pair of electrons that forms an ionic or covalent bond to the central ion. The claims as amended specify that the delivery formulation is prepared by complexing the insulin with microparticles of the

diketopiperazine derivative. Accordingly, independent claim 33, and dependent claims 34, 35, 37, and 38 are novel over Steiner.

Rejection Under 35 U.S.C. § 103

Claims 33-39 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,976,569 to Milstein ("Milstein"). Claims 40-42 were rejected under 35 U.S.C. § 103(a) as obvious over Milstein in view of the Abstract of Edelman, S.V. "Type II Diabetes Mellitus," Advances in Internal Medicine, 1998, pp 449-500) ("Edelman"). Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

a. U.S. Patent No. 5,976,569 to Milstein ("Milstein")

Milstein describes a composition comprising an active agent and at least one mono-N-substituted, di-N-substituted, or unsubstituted diketopiperazine carrier (col. 2, lines 29-32). The compositions are in the form of microspheres (col. 6, lines 65-66).

Example 25 discloses a method for encapsulating calcitonin in diketopiperazine. The method requires the co-precipitation of calcitonin and the diketopiperazine to form the microparticles. The Examiner refers to Examples 26 and 26A, which provide *in vivo* tests of these particles in fasted rats.

Like Feldstein and Steiner, discussed above, Milstein does not disclose complexing insulin to microparticles of a diketopiperazine derivative or delivery of monomeric or dimeric insulin, as required by claim 33, as amended. Milstein describes encapuslating insulin in a diketopiperazine microparticle at the same time that the microparticle is formed. However, Milstein does not describe forming a complex as by, for example, first forming diketopiperazine microparticles, and then complexing them with insulin. Further, Milstein contains no suggestion to modify its methods to prepare delivery formulations by complexing the insulin with microparticles of the diketopiperazine derivative, as required by claim 33, as amended. Finally, there is no suggestion of a delivery formulation for monomeric or dimeric insulin. Accordingly, independent claim 33 and dependent claims 34-39 are not obvious over Milstein.

b. Edelman

Edelman describes the use of combination therapy (bedtime intermediate-acting insulin in combination with daytime oral antidiabetic agents) for the treatment of Type II diabetes. Edelman states that if the combination therapy is not successful, a split-mixed regimen using premixed 70/30 insulin pre-breakfast and pre-dinner can be used. Edleman contains no discussion or suggestion of diketopiperazine microparticles, let alone complexing insulin with microparticles of a diketopiperazine derivative.

c. The combination of Milstein with Edelman

Claims 40-42 depend from independent claim 33. In order to establish a *prima facie* case of obviousness, the reference(s) must disclose or suggest each and every element of the claims.

As noted above, Milstein does not disclose or suggest complexing insulin with microparticles of a diketopiperazine derivative. Edelman does not make up for the deficiencies of Milstein. Edelstein merely broadly refers to "insulin regimes" or a "split -mixed" insulin regime. Neither Edelstein nor Milstein disclose complexing insulin with microparticles of a diketopiperazine derivative to deliver insulin monomers or dimers. Neither Edelstein nor Milstein contains a disclosure or suggestion of forming a complex. Accordingly, claims 40-42 are not obvious over Milstein in view of Edelman.

Obviousness- type Double Patenting Rejections

Claims 33-39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-7, and 10-14 of U.S. Patent No. 6,071,497 to Steiner *et al.* ("the '497 patent") and claims 1, 4-7, and 10-12 of U.S. Patent No. 6,428,771 to Steiner *et al.* ("the '771 patent"). Claims 33-35 and 39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 11-12, 15-17, and 21-26 of U.S. Patent No. 6,444,226 to Steiner *et al.* ("the '226 patent"). Claims 33-35 and 40-42 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of U.S. Patent No. 6,652,885 to Steiner *et al.* ("the '885 patent"). Applicants respectfully traverse these rejections.

Legal Standard

When determining whether the claims of an application define an invention that is an obvious variation of an invention defined in the claims of a patent, the claims of the application are compared with the claims in the patent, the disclosure in specification of the patent is not considered in the analysis (*see* MPEP §§ 800-822). The MPEP explains that "[a] double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103' except that the patent principally underlying the double patenting rejection is not considered prior art." MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (CCPA 1967). Therefore, analysis employed in an obviousness-type double patenting rejection parallels the guidelines for a 35 U.S.C. § 103 obviousness determination. *Id.*, citing *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985).

a. U.S. Patent No. 6,444,226 to Steiner et al. ("the '226 patent") and U.S. Patent No. 6,652,885 to Steiner et al. ("the '885 patent")

Without making any admissions, and solely for the purpose of facilitating prosecution, applicants are submitting a Terminal Disclaimer to obviate the double patenting rejection over the '226 patent and the '885 patent.

b. U.S. Patent No. 6,428,771 to Steiner et al. ("the '771 patent")

Claims 33-39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-7, and 10-12 of the '771 patent.

This rejection is improper based on a comparison of pending claims 33-39 with claims 1, 4-7, and 10-12 of the '771 patent as shown below.

Claims as Amended	Claims of the '771 Patent
33. A method for delivering monomeric or dimeric insulin to a patient in need thereof, comprising administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative, wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative, wherein the diketopiperazine derivative has the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl. 35. The method of claim 33 wherein X is fumaryl. 36. The method of claim 33 wherein X is succinyl. 37. The method of claim 33 wherein X is maleyl.	1. A microparticulate system for controlled drug delivery to the pulmonary system comprising: synthetic biodegradable polymeric microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter between 0.5 microns and ten microns and are formulated to release the incorporated agent at a pH of 6.0 or greater under conditions present in the pulmonary system, in a pharmaceutically acceptable carrier for administration to the lungs, and wherein the microparticles are made from a material selected from the group consisting of diketopiperazines, poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, copolymers and mixtures thereof.

38. The method of claim 33 wherein X is glutaryl. 39. The method of claim 33 wherein the composition is in a dry powder form administered to the lungs via inhalation.	4. The system of claim 1 wherein the agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids drugs, and combinations thereof. 5. The system of claim 4 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, vaccines, gene encoding adenosine deaminase, and Argatroban. 6. The system of claim 1 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs. 7. A method for controlled drug delivery to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of synthetic biodegradable polymeric microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent, wherein the microparticles have a diameter

between 0.5 microns and ten microns and are formulated to release the incorporated agent at a pH of 6.0 or greater under conditions present in the pulmonary system, in a pharmaceutically acceptable carrier for administration to the lungs, and wherein the microparticles are made from a material selected from the group consisting of diketopiperazines, poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, copolymers and mixtures thereof.

10. The method of claim 7 wherein the agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids drugs, and combinations thereof.

11. The method of claim 10 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF,

	lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β-galactosidase and Argatroban. 12. The method of claim 7 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs.

Independent claims 1 and 7 of the '771 patent are directed to a microparticulate system for controlled drug delivery to the pulmonary system comprising synthetic biodegradable polymeric microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent and methods of using thereof. Claims 1, 4-7, and 10-12 of the '771 patent do not define a microparticle, wherein insulin is complexed with microparticles of a diketopiperazine derivative, nor do they define delivering monomeric or dimeric insulin to a patient, as required by independent claim 33, as amended. Like the term "encapsulate" discussed above, "incorporating" as generally used in the art does not require a specific interaction between an agent and the particle in which it is incorporated. In contrast, "complexing" is typically used to refer to the formation of complex chemical species by the coordination of groups of atoms to a central ion, commonly a metal ion, such as when a ligand provides a pair of electrons that forms an ionic or covalent bond to the central ion. Thus, "complexing" is not obvious in view of the mere use of the term "incorporating". Accordingly, claims 33, and 35-39, as amended, are not obvious over claims 1, 4-7, and 10-12 of the '771 patent.

c. U.S. Patent No. 6,071,497 to Steiner et al. ("the '497 patent")

Claims 33-39 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 4-7, and 10-14 of the '497 patent. This rejection is improper based on a comparison of pending claims 33-39 with claims 1, 4-7, and 10-14 of the '497 patent as shown below:

Claims as Amended	Claims of the '497 Patent
33. A method for delivering monomeric or dimeric insulin to a patient in need thereof, comprising administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative, wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative, wherein the diketopiperazine derivative has the formula 2,5-diketo-3,6-di(4-X-aminobutyl)piperazine, wherein X is selected from the group consisting of fumaryl, succinyl, maleyl, and glutaryl. 35. The method of claim 33 wherein X is fumaryl. 36. The method of claim 33 wherein X is	1. A microparticulate system for drug delivery to the pulmonary system comprising: synthetic biodegradable microparticles which comprise a diketopiperazine and which have a diameter between 0.5 microns and ten microns and which release an incorporated therapeutic, prophylactic, or diagnostic agent at a pH of 6.0 or greater, in a pharmaceutically acceptable carrier for administration to the lungs. 4. The system of claim 1 wherein the therapeutic, prophylactic or diagnostic agent is selected from the group consisting of proteins, polysaccharides, lipids, nucleic acids, other synthetic organic pharmaceutical compounds, and combinations thereof. 5. The system of claim 4 wherein the agent is selected from the group consisting of insulin,

succinyl. 37. The method of claim 33 wherein X is maleyl. 38. The method of claim 33 wherein X is glutaryl. 39. The method of claim 33 wherein the composition is in a dry powder form administered to the lungs via inhalation.	calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, vaccines, gene encoding adenosine deaminase, and Argatroban. 6. The system of claim 1 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs. 7. A method for delivery of particles to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of synthetic biodegradable microparticles which comprise a diketopiperazine and which have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs. 10. The method of claim 7 wherein the microparticles further comprise a therapeutic, prophylactic, or diagnostic agent selected from the group consisting of proteins,

polysaccharides, lipids, nucleic acids, other synthetic organic pharmaceutical compounds, and combinations thereof.

11. The method of claim 10 wherein the agent is selected from the group consisting of insulin, calcitonin, felbamate, heparin, parathyroid hormone and fragments thereof, growth hormone, erythropoietin, AZT, DDI, G CSF, lamotrigine, chorionic gonadotropin releasing factor, luteinizing releasing hormone, β.-galactosidase and Argatroban.

12. The method of claim 7 wherein the microparticles are a dry powder provided with an apparatus for administration of the microparticles to the lungs.

13. The system of claim 1 wherein the therapeutic, prophylactic, or diagnostic agent is selected from the group consisting of vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, antibiotics, antivirals, antisense, antigens, and antibodies.

14. The method of claim 7 wherein the

	therapeutic, prophylactic, or diagnostic agent is selected from the group consisting of vasoactive agents, neuroactive agents, hormones, anticoagulants, immunomodulating agents, cytotoxic agents, antibiotics, antivirals, antisense, antigens, and antibodies.

Claims 1 and 7 of the '497 patent are directed to a microparticulate system for drug delivery to the pulmonary system comprising synthetic biodegradable microparticles which comprise a diketopiperazine, have a diameter between 0.5 microns and ten microns and release an incorporated therapeutic, prophylactic, or diagnostic agent and methods of using thereof. Claims 1, 4-7, and 10-14 of the '497 patent do not define a microparticle, wherein insulin is complexed with microparticles of a diketopiperazine derivative, nor do they define delivering monomeric or dimeric insulin to a patient, as required by independent claim 33, as amended. Like the term "encapsulate" discussed above, "incorporate" as generally used in the art does not require a specific interaction between an agent and the particle in which it is incorporated. In contrast, "complexing" is typically used to refer to the formation of complex chemical species by the coordination of groups of atoms to a central ion, commonly a metal ion, such as when a ligand provides a pair of electrons that forms an ionic or covalent bond to the central ion. Thus "complexing" is not obvious in view of the mere use of the term "incorporated" in claim 1 of the '497 patent.

Claim 7 of the '497 patent, and its dependent claims, do not even specify that the diketopiperizine microparticles "incorporate" an active agent. Claim 7 merely requires administering an effective amount of synthetic biodegradable microparticles which comprise a diketopiperazine and have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs. Dependent claims, such as claim 8, specify that the microparticles further comprise a therapeutic, prophylactic, or diagnostic agent selected from a list of agents. "Comprise" is a standard term used in claims to indicate that a method or composition contains the listed subject matter and may contain additional, non-listed subject matter. Similar to the discussion above regarding the term "incorporate", the mere statement that microparticles "comprise" both a diketopiperazine and a particular agent, does not require a specific interaction between an agent and the microparticle. Thus, "complexing" is not obvious in view of the mere use of the term "comprise". Additionally, claims 1, 4-7, and 10-14 of the '497 patent do not disclose delivering monomeric or dimeric insulin to a patient. Accordingly, claims 33, and 35-39, as amended, are not obvious over claims 1, 4-7, and 10-14 of the '497 patent.

Provisional Obviousness- type Double Patenting Rejections

Claims 33-39 and 42 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 23-36 of copending U.S.S.N. 10/706,243 ("the '243 application") and claims 1-5, 8-10, 16-17, 23-24, 26-30, and 36 of copending U.S.S.N. 11/210,710 ("the '710 application"). Claims 33-35 and 40-42 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5 and 17-23 of

copending U.S.S.N. 11/329,686 ("the '686 application"). Applicants respectfully request that the provisional rejections be held in abeyance until such time as claims are determined to be allowable or issue in the copending applications.

Allowance of claims 33, and 35-42, as amended, is respectfully solicited.

Respectfully submitted,

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